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PERFORMANCE STUDIES ON ANIMALS EXPOSED TO EXTERNAL RADIATION

PART III. FURTHER STUDIES OF THE EFFECTS OF X IRRADIATION UPON THE PERFORMANCE OF RATS IN A DAILY EXHAUSTIVE EXERCISE TEST

PART IV. THE RELATIONSHIP BETWEEN THE NUMBER OF POST-IRRADIATION EXERCISE TRIALS AND LETHALITY IN ANIMALS EXPOSED TO ROENTGEN RAYS

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ABSTRACT USNRDL-390

The effect of whole body X irradiation on intensive exercise performance by male rats was observed for several weeks following irradiation. Swimming to exhaustion was the performance test used. Animals were tested daily, 5 times per week, for 2 weeks prior to irradiation, and, on the same test schedule, for as long as 9 weeks post-irradiation.

Exposure to X-ray doses of 300 to 1,000 r depressed the ability to perform. The magnitude of the depression in performance was dependent upon the X-ray dose. Irradiated animals surviving the period of testing recovered sufficiently by the ninth week after irradiation to attain their pre-irradiation performance level although they were not identical in performance with concurrently tested non-irradiated animals. Animals which died soon after irradiation were nearly normal in performance prior to death; animals which died later had a lower performance level varying with the length of the post-irradiation survival period.

In a second series of tests, rats were exercised to exhaustion daily, 5 times per week, for 2 weeks prior to irradiation, and then divided into 6 groups and irradiated with 500 r of X rays. The groups were then subjected to various numbers of post-irradiation daily-exercise trials, and the survival rates for each group were compared with that for non-exercised irradiated control animals. It was found that repeated exercise during the first 3 weeks after irradiation increased radiation mortality in proportion to the total number of exercise trials. Continuation of exercise beyond this period resulted in no further increase in radiation mortality.

PERFORMANCE STUDIES ON ANIMALS EXPOSED TO EXTERNAL RADIATION

III. FURTHER STUDIES OF THE EFFECTS OF X IRRADIATION UPON THE PERFORMANCE OF RATS IN A DAILY EXHAUSTIVE EXERCISE TEST

INTRODUCTION

There have been few studies reported concerning the effects of ionizing radiations upon the ability of animals to perform in tests of physical endurance. Stapleton and Curtis[1] reported that the performance of mice in a forced exercise test was appreciably reduced by exposure to a mid-lethal dose of fast neutrons. The effect was observed soon after irradiation and continued irreversibly for 300 days of observation. McKeen, et al.,[2] detected a slight transitory decrease in swimming endurance of rats in a study limited to the first 15 days after irradiation.

The first part of this report summarizes the effects observed in the performance of rats in a standardized exhaustive swimming exercise test following single acute doses of X rays. Data from previously reported experiments[3,4] are included in order to describe more completely the relationship between radiation exposure dose and performance ability.

EXPERIMENTAL PROCEDURES

USNRDL-390

In each of five experiments a control and one or more irradiated groups were exercised during a 2 week pre-irradiation test period to accommodate the animals to the test conditions and to establish an individual base performance time for each animal. Animals were then irradiated or sham-irradiated (controls) and their performance was tested for several post-irradiation weekly periods. Each weekly period

consisted of five consecutive daily trials in which the animal was required to swim to exhaustion. In order to provide information concerning alterations in body weight and radiation lethality, additional groups of non-irradiated animals and non-exercised irradiated animals were included in each experiment.

In describing changes of performance, all swimming times for each individual were calculated as percentages of the individual's average swimming time for the second week, and from these values the reported weekly mean performances for each group were compiled. In this manner each irradiated animal served as its own control, and the extent of relative change in performance among different animals could be compared. In addition, the performance of groups of irradiated animals was compared with that of groups of non-irradiated animals for corresponding swimming trials.

The X-ray doses (air) used were 300, 500, 600, 700, 860, and 1,000 r. Animals irradiated with 300 and 500 r were swum concurrently with the same non-irradiated control group. Each of the other irradiated groups was studied in an individual experiment and compared with a concurrently tested non-irradiated control group.

Animals were irradiated immediately prior to the eleventh swimming trial, which was on the first day of the third week of testing. The day of irradiation was designated as day one post-irradiation in presenting the swimming performance, body weight, and survival data.

Adult male rats of the Sprague-Dawley strain, bred in the Laboratory colony, were used throughout the study. In each experiment, all animals were from litters born during the same week and were of similar body weight. Purina Laboratory Chow and water were supplied _ad lib._ except that food was withdrawn 2 hours prior to each swimming trial. Animals were caged individually and were weighed at least twice a week throughout the study.

Performance Test Procedure. In the performance tests, rats swam individually in 24-gallon cylindrical metal tanks filled with fresh water to a constant level. These tanks were thoroughly cleaned and refilled each day. In each experiment the water temperature was adjusted within ± 1.5 C of a given temperature in the range of 15 to 21 C. A 10 gram lead weight was clipped to the chest fur of the test animals during each swimming trial, except in the 860 r dose study in which a 15 gram weight was used. Animals swam until they sank and remained below a line approximately 18 inches beneath the surface of the water for a period estimated to be longer than 30 seconds. The animals were then retrieved, and the total performance time for each individual was

recorded to the nearest minute. The use of this technique was assumed to result in exhaustion, since the animals showed many signs of marked fatigue such as the inability to maintain normal posture, to walk, or to swim further if returned to the tank immediately following completion of an exercise trial. Using this technique the mean performance time for the second-week trials was 16 minutes among 236 animals tested. Occasionally, an animal floated or exhibited other abnormalities in swimming, and the trial had to be discarded.

Irradiation Procedure. The radiation factors were as follows: X rays, 250 KVP; 15 ma; filter, 0.5 mm Cu + 1.0 mm Al (HVL 1.5 mm Cu); TSD, 40 inches; 25 r/minute (air dose) measured with Victoreen thimble chambers. For exposure to the X-ray beam, animals were placed in Lucite chambers constructed to approximate an isodose surface. The chambers were spaced radially on a motor-driven turntable which revolved slowly in the radiation field. Non-irradiated exercised animals were confined in the irradiation chambers for the same length of time as the irradiated exercised animals.

RESULTS

In the analysis of data, the performance of irradiated animals surviving for the entire period of study was considered separately from that of animals which succumbed during the same period.

The weekly mean performances for each group are summarized in Table 1. In general, a gradual improvement with successive weeks of testing was observed among non-irradiated groups. Following irradiation, the performance level of irradiated animals surviving the experiment decreased, passed through a minimum during the third or fourth week, and then increased throughout the remainder of the study. The magnitude of this depression was dependent upon the size of the X-ray dose, as shown in Fig. 1. The apparent effect of 300 r upon performance may not be significant. The median test described by Moses[5] was used to determine the chance probability for differences as large as those observed between controls and groups irradiated with 300 and 500 r for each week after irradiation. Performance of the group irradiated

TABLE 1

Weekly Performance, by Group, of Rats Subjected to Various X-ray Doses Where Performance Times Are Expressed as Percentage of the Second-week Mean Performance Time

Week of Test[(a)]	Performance (per cent ± S. D.[(b)])													
	300 r		500 r[(c)]		600 r			700 r			860 r		1,000 r	
	Non-irrad. Controls	Irrad. Survivors	Irrad. Survivors	Irrad. Non-survivors	Non-irrad. Controls	Irrad. Survivors	Irrad. Non-survivors	Non-irrad. Controls	Irrad. Survivors	Irrad. Non-survivors	Non-irrad. Controls	Irrad. Non-survivors	Non-irrad. Controls	Irrad. Non-survivors
	(n = 19)	(n = 18)	(n = 14)	(n = 8)	(n = 10)	(n = 7)	(n = 7)	(n = 25)	(n = 2)	(n = 25)	(n = 24)	(n = 23)	(n = 23)	(n = 24)
1	96±18	97±13	100±21	92±15 (8)	83±13	87±20	90±21 (7)	91±16	96±10	95±15 (25)	79±12	75± 9 (33)	79±12	73±12
2	100 -	100 -	100 -	100 - (8)	100 -	100 -	100 - (7)	100 -	100 -	100 - (25)	100 -	100 - (33)	100 -	100 -
3[(a)]	95±11	100±11	96±16	93±15 (8)	97±12	117±18	116±22 (7)	99±12	107±18	115±15 (25)	115±19	117±21 (32)	100±13	97±11
4	96±14	93±14	88±12	76±10 (6)	106±16	85±11	88±33 (7)	111±23	75±15	88±24 (21)	110±23	65±11 (3)		
5	100±16	92±12	83±19	74±10 (3)	114±14	69±16	74±32 (5)	117±26	64±12	56±23 (4)				
6	107±20	96±16	80±22	80±12 (2)	104±13	67±14	55±19 (2)	121±25	48±13					
7	109±22	100±20	84±20	67 - (1)	115±23	83±16	67 - (1)	119±28	58±14					
8	107±22	101±16	88±19		118±19	91±18	64 - (1)	119±20	78±12					
9	104±24	98±16	91±22		111±20	85±18								
10	107±21	100±17	97±23		115±27	105±25								
11	114±23	108±20	106±24		116±18	104±19								

(a) Rats were irradiated on the first day of the third week.

(b) Standard deviation, $\sqrt{\Sigma d^2/n-1}$, is based upon the distribution of the weekly means of individual animals about the group mean. n is the number of animals exposed to the test conditions daily during each week. In the case of non-surviving irradiated animals n decreased after irradiation to the number of survivors for each week indicated in parentheses.

(c) The same non-irradiated controls were used with both the 300 and 500 r studies.

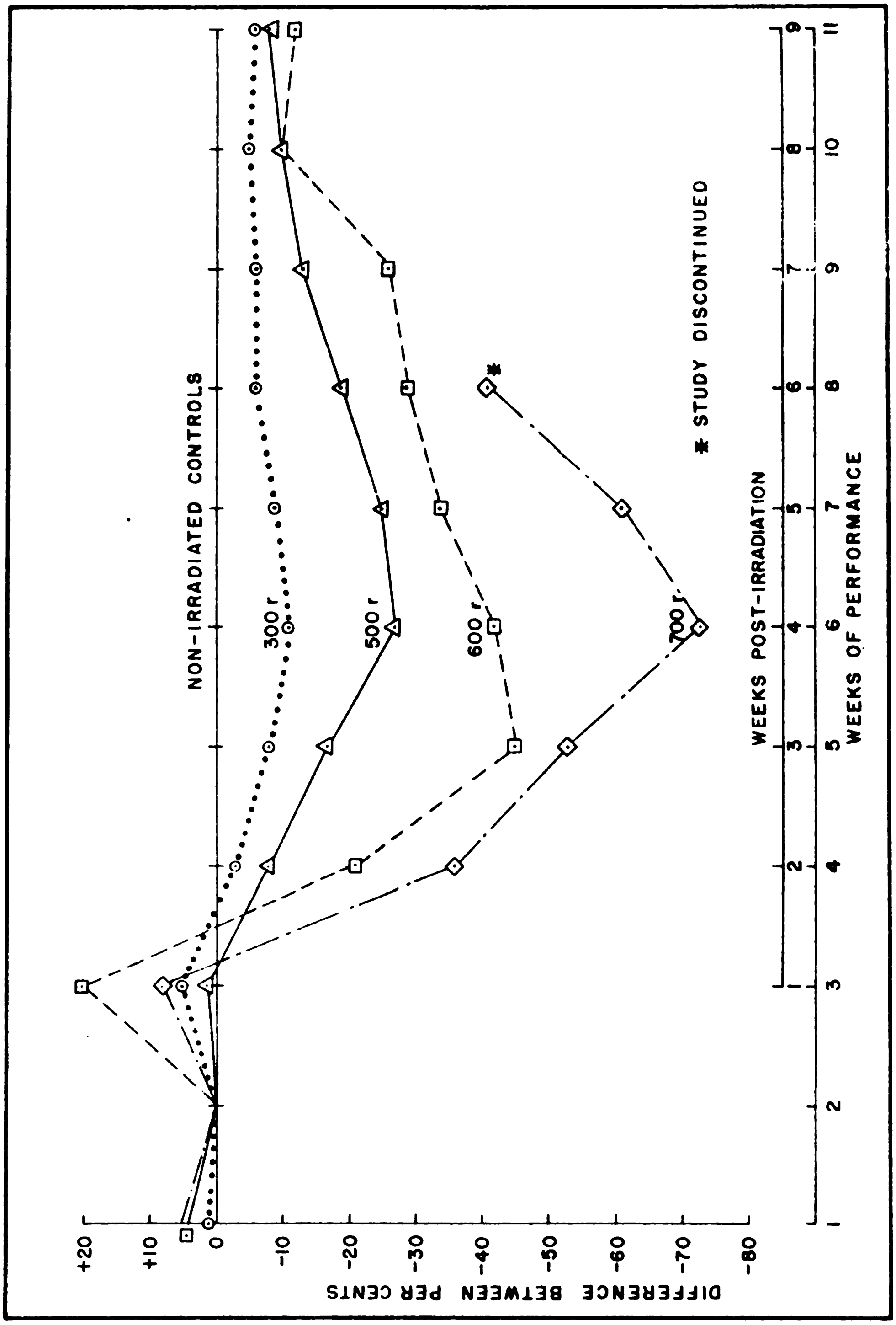

Fig. 1 The Difference in Performance between Non-Irradiated and Surviving Irradiated Groups for Each Week

with 300 r was not significantly different from that of the controls ($p > 0.05$). However, it is interesting to note that performance following 300 r appeared lower than that of the controls during 8 of the 9 weeks post-irradiation (Table 1). Performance following 500 r was significantly lower than that of the controls during the fourth and fifth weeks post-irradiation.

Animal groups exposed to 300, 500, and 600 r had recovered sufficiently by the ninth week post-irradiation to attain their pre-irradiation performance (Table 1) although they were not identical in performance with their non-irradiated controls (Fig. 1). Although only 2 of the 27 animals exposed to 700 r survived 6 weeks of performance after irradiation, these survivors showed the same trend in performance illustrated by the survivors of smaller X-ray doses.

It is difficult to interpret the information gained by averaging the performance times of non-surviving irradiated animals because the composition of the group is changed with each death. The trend in the performance of non-surviving irradiated animals resembles that for survivors of the same X-ray dose during the initial 4 weeks after irradiation (Table 1). Examination of individual records shows that animals which died soon after irradiation were nearly normal in performance; animals which died later had, prior to death, a lower performance level which varied with the length of the post-irradiation survival period. This relationship between performance and survival time is indicated by the plot of the performance during the week of death against the length of the post-irradiation survival period shown in Fig. 2.

Changes in body weight with irradiation and/or daily exercise were observed during the course of the study. Weight alterations with exposure to 600 r are summarized graphically in Fig. 3 to illustrate the changes which occurred with daily exercise, with irradiation, and with irradiation followed by daily exercise. The body weight on the day of irradiation was used as a base weight for each animal, and the subsequent weights were calculated as percentages of this base weight. The group averages are presented in Fig. 3. The effect of daily exhaustive exercise was to prevent the normal increment in weight shown by non-exercised animals. The effect of irradiation on growth rate of exercised and non-exercised animals appears to be transient since, following an initial post-irradiation weight loss, growth rates exhibited by both groups of irradiated animals appear to be similar to their respective non-irradiated control groups.

Mean weight changes for groups of non-surviving irradiated animals are not very meaningful since data must be pooled from animals which died on different days following irradiation. Some of the exercised and non-exercised irradiated animals that died began to gain weight prior

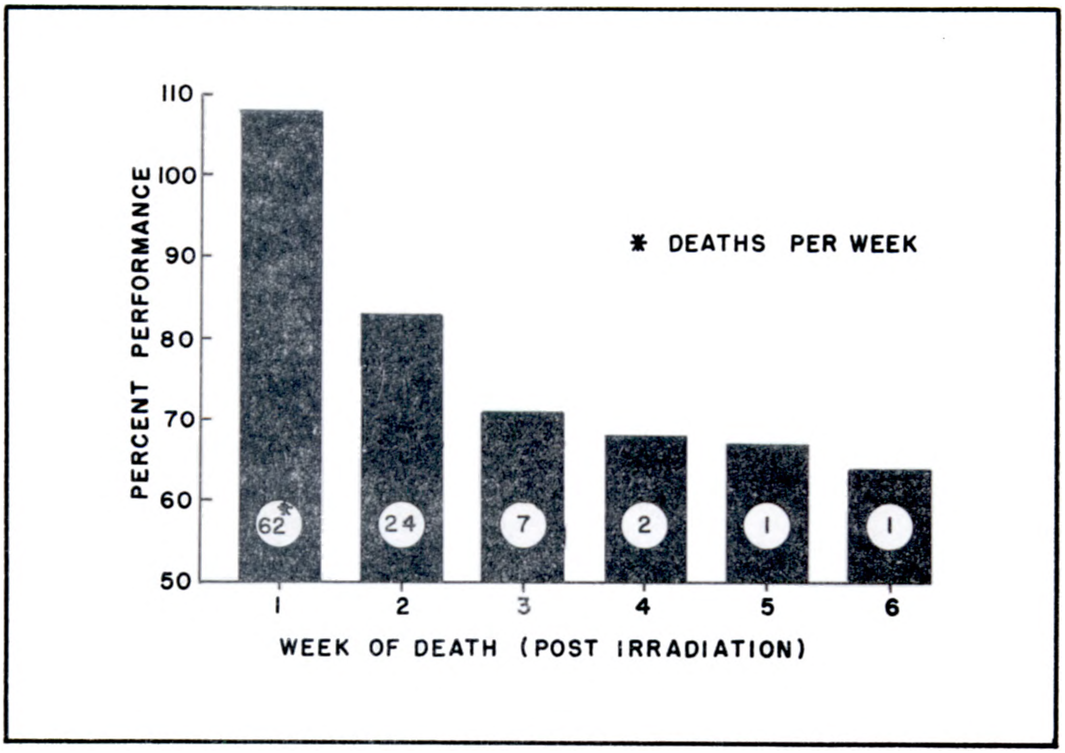

Fig. 2 Performance of Non-survivors during the Week of Death as a Function of Post-irradiation Survival Time. Values Are the Means for All Animals Dying during a Given Week Regardless of Radiation Dose.

to death while others survived the initial loss to regain some weight but died during a second decline. Johnson, et al.,[6] have reported a similar weight pattern for irradiated rats on controlled diets.

The effect of daily exercise upon the mortality of irradiated animals was similar to that previously observed.[7] The survival rates of exercised and non-exercised animals irradiated simultaneously are summarized in Table 2. As measured by the resulting decrease in survival, the irradiated animals were sensitive to the stress of daily exhaustive exercise in the swimming performance test.

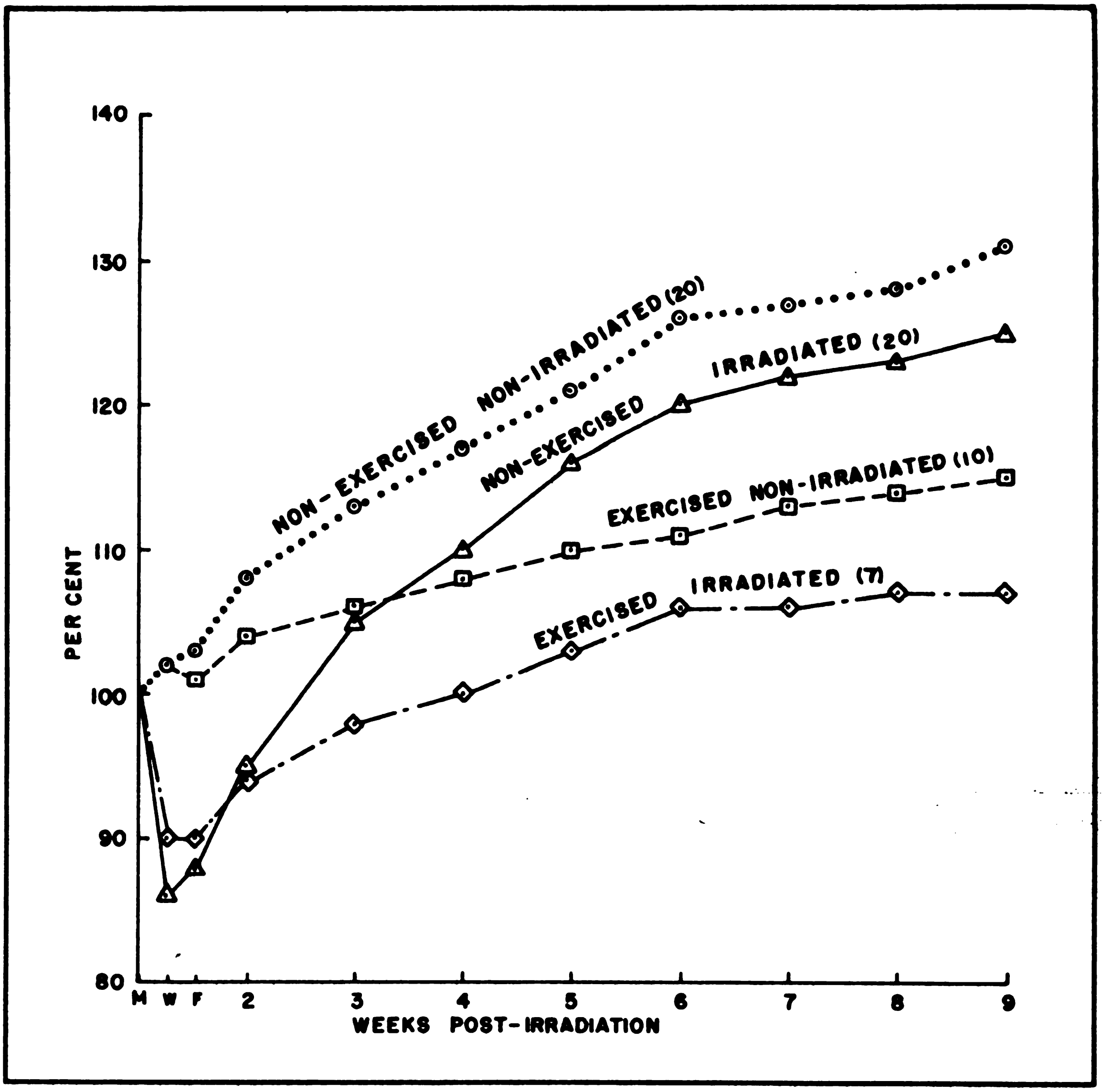

Fig. 3 Group Mean Body Weights for Rats Surviving 600 r in Percentage of Weight on the Day of Irradiation. The Number of Animals Comprising Each Group Is Indicated in Parentheses.

TABLE 2

Survival Rates of Exercised and Non-exercised Irradiated Rats

Dose (r)	Post-irradiation Observation Period (days)	Non-exercised Irradiated			Exercised Irradiated		
		No. Observed	No. Surviving	Survival (per cent)	No. Observed	No. Surviving	Survival (per cent)
300	63	30	30	100	18	18	100
500	63	30	27	90	22	14	64
600	63	20	20	100	14	7	50
700	42	38	25	66	27	2	7
860	30	30	5	17	33	0	0
1,000	14	25	0	0	24	0	0

DISCUSSION

The results of the present study demonstrate that the performance of intensive physical effort reflects the injurious effects of total body X irradiation. The change in performance is related to the severity of the radiation dose. Both surviving and non-surviving irradiated animals showed a decreased capacity to perform although death was not necessarily preceded by poor performance. Animals which died soon after irradiation had better performance times during several trials prior to death than those which survived longer after irradiation. In this regard it is of interest to note that, after doses of X rays in the high lethal range, 860 and 1,000 r, performance ability was maintained for the first week following irradiation although the majority of animals died during that time.

Among survivors it can be observed that, regardless of the magnitude of change in performance ability, the period of lowest performance was similar for all doses of X rays. The recovery rates in performance

ability were such that surviving irradiated groups attained their pre-irradiation performance levels by the ninth week post-irradiation.

Exercise did not increase the magnitude of body weight loss which characteristically occurs following irradiation, nor did exercise alter the time of occurrence of weight loss. The significance of the relationship between the changes in body growth and performance is not clear since the poorest performance occurred during the period of weight recovery and not at the time of maximum weight loss.

It is difficult to correlate changes in performance with other injuries known to occur after irradiation. Studies concerned with radiation injury in rats resulting from single exposures to X rays have indicated that many physiological processes are restored to normal activity by 30 days post-irradiation. The erythrocyte count, however, is very low during the third and fourth weeks post-irradiation[8] and corresponds to the period of reduced performance in the present study. This suggests that the oxygen transport presumed necessary for peak physical performance may be lacking because of the marked oligocythemia occurring at this time.

Many of the physiological changes occurring with repeated or prolonged effort in work performance tests are those of adrenal insufficiency.[9,10] Undoubtedly this form of exhaustive exercise represents a severe stress to the irradiated animal. This is reflected in irradiated animals by the depressed rate of body weight recovery and increased mortality following exercise as well as by poor performance. It may be that changes in performance in the present test are referable to changes in the irradiated animal's ability to cope with repeated stress and are not specific to exercise.

SUMMARY USNRDL-390

Rats were required to perform daily in a standardized exhaustive exercise test (swimming) 5 times per week for periods as long as 9 weeks after X irradiation. Exposure to X-ray doses of 300 to 1,000 r depressed the ability to perform in this test. The magnitude of depression in performance was dependent upon the size of the X-ray dose.

Irradiated animals surviving the period of testing recovered sufficiently by the ninth week after irradiation to attain their pre-irradiation performance levels although they were not identical in performance with concurrently tested non-irradiated animals. Animals which died soon after irradiation were nearly normal in performance prior to death; animals which died later had a lower performance level varying with the length of the post-irradiation survival period.

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PERFORMANCE STUDIES ON ANIMALS EXPOSED TO EXTERNAL RADIATION

IV. THE RELATIONSHIP BETWEEN THE NUMBER OF POST-IRRADIATION EXERCISE TRIALS AND LETHALITY IN ANIMALS EXPOSED TO ROENTGEN RAYS

INTRODUCTION USNRDL-390

There have been relatively few studies in which irradiated animals have been subjected to single or repeated challenges at various times after irradiation in order to characterize the period of altered resistance resulting from irradiation. The tolerance of irradiated mice to KCl and to histamine injections has been observed to increase and then decrease during the first 5 days after irradiation.[1] Irradiated mice have been shown to be less resistant to trauma at 28 days post-irradiation,[2] less sensitive to progressive hypoxia throughout 19 days following irradiation,[3] and more susceptible to infection than non-irradiated controls.[4] The inclusion of ACTH[5] or of thyroid[6] in the diet has been shown to decrease survival following irradiation. Resistance to the challenge of exposure to simulated altitudes up to 25,000 feet,[7] and even up to 40,000 feet for acute exposure,[8] has been studied over a period of several weeks after irradiation, but no differences between irradiated and non-irradiated animals were observed.

Since it was reported previously[9] that when animals are exercised, after irradiation, by swimming to exhaustion daily there results a greater mortality than with irradiation alone, it became of interest to determine the relationship existing between the number of daily post-irradiation exercise trials and the extent of increase in mortality following irradiation and exercise. The following series of experiments was carried out in an attempt to elicit this information.

EXPERIMENTAL PROCEDURES USNRDL-390

The exhaustive exercise procedures were identical with those described in Part III, with the exception that the number of post-irradiation daily-exercise trials was specifically designated, and no swimming times were

recorded. Following the 2 week pre-irradiation test period of 10 trials necessary for accommodation to the test, the animals were irradiated, then subjected either to no (SIN), one (SIS-1), five (SIS-5), ten (SIS-10), fifteen (SIS-15), or twenty (SIS-20) post-irradiation exhaustive daily-exercise trials. The survival rate for each group was compared with that of simultaneously irradiated non-exercised controls (NIN). Immediately prior to the eleventh swimming trial, which was on the first day of the third week of testing, all animals were irradiated with 500 r of X rays. The radiation factors were as follows: X rays, 250 KVP; 15 ma; filter, 0.5 mm Cu + 1.0 mm Al (HVL 1.5 mm Cu); TSD, 40 inches; 25 r/minute (air dose) measured with Victoreen thimble chambers.

In view of the limited number of animals which could be exercised concurrently, several experiments, identical with respect to irradiation dose and to daily-exercise procedures, were carried out. The results reported are the grouped data for all of these experiments. In summarizing the survival data, groups ultimately subjected to different numbers of post-irradiation daily-exercise trials were considered identical up to the point where a given group was retired from further exercise. The median test described by Moses[10] was used to estimate the probability of chance occurrence of the differences observed in 30 day survival rates among the groups subjected to different numbers of exercise trials.

RESULTS

From the survival curves shown in Fig. 1, it is apparent that the 30 day survival rates for animals exercised after irradiation (all SIS groups) were found to be lower than the survival rates for animals subjected to no post-irradiation exercise (NIN, SIN groups). The probabilities of chance occurrence of the observed differences in 30 day survival rates among the several groups (Fig. 1) indicate that there are statistically significant differences between either NIN or SIN and all groups exercised after irradiation except the SIS-1; between SIS-1 and SIS-10, -15 or -20; and between SIS-5 and SIS-15 or -20. Since deaths occurred as late as 28 days post-irradiation in the SIS-20 group, these animals were held for several weeks after the usual 30 days post-irradiation, but no further mortality was observed.

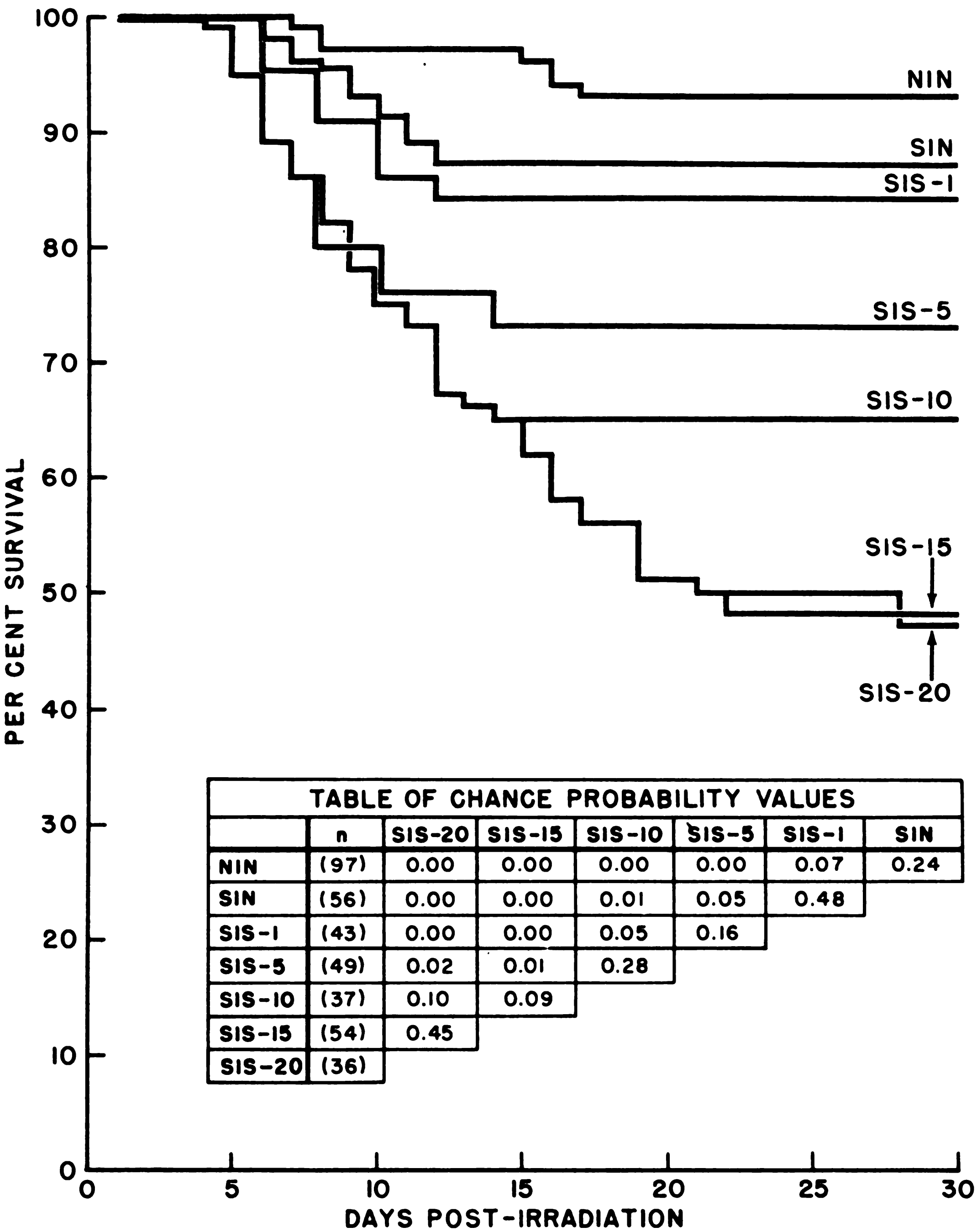

TABLE OF CHANCE PROBABILITY VALUES							
	n	SIS-20	SIS-15	SIS-10	SIS-5	SIS-1	SIN
NIN	(97)	0.00	0.00	0.00	0.00	0.07	0.24
SIN	(56)	0.00	0.00	0.01	0.05	0.48	
SIS-1	(43)	0.00	0.00	0.05	0.16		
SIS-5	(49)	0.02	0.01	0.28			
SIS-10	(37)	0.10	0.09				
SIS-15	(54)	0.45					
SIS-20	(36)						

Fig. 1 Percentage Survival of 500 r Irradiated Animals Subjected to Various Numbers of Post-irradiation Exercise Trials

There is no appreciable effect of pre-irradiation exercise upon the 30 day survival rate of irradiated animals, as indicated by the relatively high probability ($p = 0.24$) of chance occurrence of the observed difference between the NIN and SIN groups.

As shown in Fig. 2, exercise effectively lowered the 30 day survival rate of irradiated animals when undertaken during the first 3 weeks after irradiation, but no further decrease in survival rate resulted from further exercise beyond this period. In addition, during the 3 weeks following irradiation, the extent of decrease in the 30 day survival rate of irradiated animals was proportional to the number of exercise trials, as indicated by the nearly uniform slope of the graph during this period. Although most obvious at 30 days post-irradiation, the survival rate throughout the 3 weeks following irradiation was generally proportional to the number of post-irradiation exercise trials (Fig. 1).

DISCUSSION

The results obtained in the present series confirm the previous conclusion[9] that the survival rate of irradiated animals is decreased by the challenge of daily post-irradiation exhaustive exercise but is not appreciably affected by pre-irradiation exercise.

From the present investigation it appears that there is a period of about 3 weeks following irradiation during which the irradiated animal is particularly sensitive to the challenge of repeated exhaustive exercise. Thus this sensitivity to exercise induced by irradiation does not appear to extend appreciably beyond the time interval during which radiation deaths would be expected to occur in non-exercised animals. These results are in relative agreement, with respect to the time of sensitivity, with those of Smith and Smith,[6] who described the period from the seventh to the fourteenth day post-irradiation as the critical interval during which thyroid was particularly effective in decreasing the survival rate of irradiated mice. Present results are in even closer agreement with the sensitive period reported by Schechmeister, Bond, and Swift[4] who found that the period of particular susceptibility of irradiated mice to bacterial infection extended from the third to the eighteenth day after irradiation. Chapman, et al.,[2] however, found

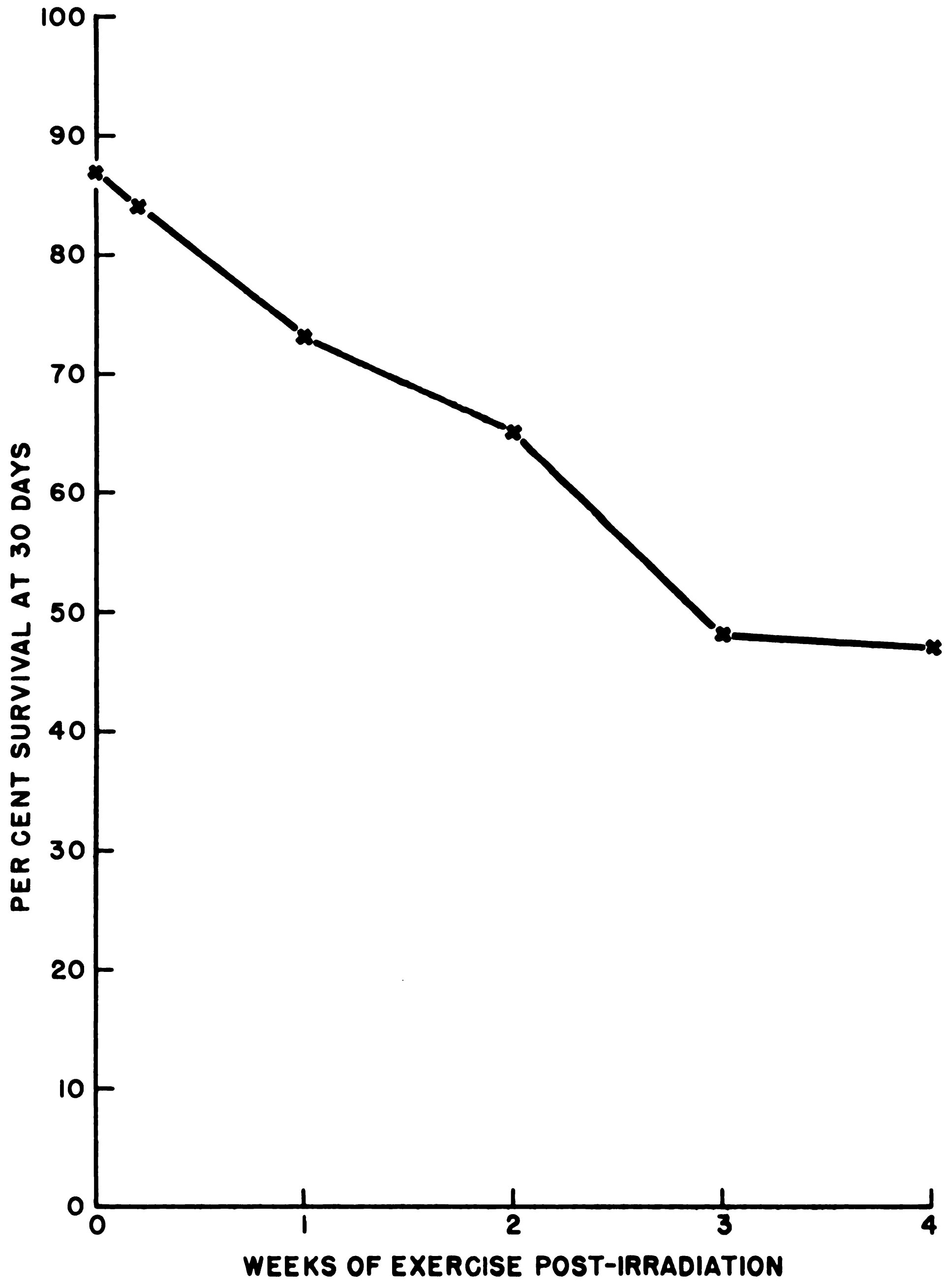

Fig. 2 Percentage Survival at 30 Days Post-irradiation as a Function of the Number of Weeks of Exercise after 500 r X Irradiation

that irradiated animals subjected to trauma in the Noble-Collip wheel at 28 days post-irradiation exhibited a lower survival rate than non-irradiated controls. The latter two studies are not entirely comparable with the present investigation, since animals were subjected only to a single challenge after irradiation.

Supporting evidence for the observation that post-irradiation sensitivity to repeated challenge does not appear to extend beyond the period during which deaths would be expected to occur among control animals can be found in the previous report on exhaustive exercise,[9] and in the studies of exposure to environmental cold carried out by Kimeldorf and Newsom.[11] In these investigations of repeated or continuous post-irradiation challenge, it was found that the survival time of challenged irradiated animals which died was generally equal to or less than that for control irradiated animals.

The direct, nearly linear proportionality between the extent of decrease in survival rate and the number of exercise trials during the first 3 weeks post-irradiation found in the present study indicates that there is no particular time during this sensitive period which is especially critical with respect to the challenge of repeated exercise. In the study previously noted,[4] using single exposures to infection as a challenge, the investigators found an increasing sensitivity of irradiated mice to bacterial infection during the first 15 days after irradiation, followed by an exponential reduction in the extent of increased sensitivity. With respect to relative changes in sensitivity with time, the results of these two studies are not necessarily inconsistent, since the two challenges differed with respect to both type and schedule.

From the foregoing discussion, it appears that the interrelationships between survival after irradiation and various additional experimental treatments or challenges may be quite complex and comparisons among various studies are difficult to make. Not only is the specific nature of the challenge probably of importance, but within a single general category of treatment the elements of time relative to irradiation, intensity, duration, and continuity of treatment are important factors which may alter the effect of the challenge. In fact, there is no assurance that the nature of the effects observed are the same in the irradiated and the irradiated-challenged animals.

SUMMARY **USNRDL-390**

Rats were exercised to exhaustion daily, 5 times per week, for 2 weeks prior to irradiation, and then divided into six groups and irradiated with an X-ray dose of 500 r. These groups were subjected to various numbers of post-irradiation daily-exercise trials, and the survival rates for each group were compared with that for non-exercised irradiated control animals. The previous observation that survival in irradiated animals is decreased by post-irradiation exhaustive exercise but not by pre-irradiation exercise was confirmed. Repeated exercise during the first 3 weeks after irradiation increased radiation mortality in proportion to the number of exercise trials. Continuation of exercise beyond this sensitive period resulted in no further increase in radiation mortality.

Approved by:

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For the Scientific Director

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